REMARKS

Applicants wish to thank the Examiner for the telephonic interview of January 7, 2008, in which the Examiner clarified that cyclosporin and rapamycin are the elected species currently under consideration. Claims 145, 147, and 149-154 are pending in the application. Claims 145 and 154 have been amended. No new matter has been introduced.

Amendment or cancellation of claims should in no way be construed as an acquiescence, narrowing, or surrender of any subject matter. Amendments or cancellations have been made not only to point out with particularity and to claim the present invention, but also to expedite prosecution of the present application. Applicants reserve the option to prosecute the originally filed claims further, or similar ones, in the instant or subsequently filed patent applications.

Priority

The Examiner has objected to the introduction of the language "wherein an inhibitor of the CD40 or CD40 ligand costimulatory interaction is not administered to the transplant recipient." Specifically, the Examiner contends that neither the priority documents (U.S.S.N. 09/249,011, now U.S. Patent No. 6,972,125; and U.S.S.N. 09/339,596, now U.S. Patent No. 6,913,747) nor the instant specification provide sufficient written description of the amended claim language. The Examiner further contends that "anti-CD40 antibodies were the only clear designation of a possible inhibitor of CD40:CD40 ligand interactions in the priority documents". With respect to the earliest priority document (U.S.S.N. 09/249,011, now U.S. Patent No. 6,972,125), the Examiner alleges that the meaning of the term "α CD40 ligands" (column 18, lines 40-41) is unclear.

Applicants respectfully traverse, and maintain that the meaning of the term "α CD40 ligands" is clear and definite. The term "α CD40 ligands" refers to a ligand that binds to CD40, including anti-CD40 antibodies and soluble forms of CD40 ligand that block CD40 signaling. While the Examiner has noted that antibodies may be agonistic or antagonistic, Applicants point out that anti-CD40 antagonistic antibodies were known in the art at the time of filing. For example, Lederman *et al.* (U.S. Patent No. 5,474,771) discloses anti-CD40 antibody 5c8, which "inhibits T cell activation of B cells." Moreover, as the Examiner has noted, "monomeric

CD40L is considered antagonistic" (page 4, line 9 of the Office Action). In addition, a skilled artisan would readily recognize that administering a soluble form of a receptor would also antagonize signaling in a particular pathway. Evidence that the latter concept was known to a person of ordinary skill in the art at the time of filing may be found, for example, in Alegre, *et al.*, *Immunomodulation of transplant rejection using monoclonal antibodies and soluble receptors*, Digestive Diseases and Sciences, 1995, 40: 58-64 (emphasis added), which was cited in the Information Disclosure Statement filed February 3, 2003 and listed in the References Cited of the earliest priority document (U.S.S.N. 09/249,011, now U.S. Patent No. 6,972,125).

In view of the foregoing, Applicants submit that, given the knowledge available in the art at the time of filing, priority document U.S.S.N. 09/249,011 (now U.S. Patent No. 6,972,125) is enabling, at least, for the administration of anti-CD40 antibodies, soluble CD40 ligand, and CD40 receptor. Solely for the purpose of expediting prosecution and in no way conceding to the Examiner's rejections, Applicants have amended claims 145 and 154, rendering the Examiner's objection moot. Applicants therefore request reconsideration and withdrawal of the objection.

Rejection of Claims 145, 147[1], and 149-154 Under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected claims 145, 147, and 149-154 under 35 U.S.C. § 112, first paragraph, as allegedly not conveying to one of ordinary skill in the art that Applicants were in possession of the claimed invention. Specifically, and as set forth above, the Examiner reiterates the allegation that the priority documents and instant specification do not "provide sufficient written description of the newly amended claim limitation 'wherein an inhibitor of the CD40 or CD40 ligand costimulatory interaction is not administered to the transplant recipient,' as broadly claimed in the instant claims."

Applicants respectfully traverse the rejection. However, solely in order to expedite prosecution and in no way conceding to the Examiner's rejections, Applicants have amended the claims, thereby rendering the Examiner's rejection moot. Applicants therefore respectfully request reconsideration and withdrawal of the rejection.

[1] In the Office Action, the Examiner lists claims 145-147 in the rejection. Applicants respectfully point out that claim 146 was canceled in the response filed September 25, 2007.

Rejection of Claims 145, 147, and 154 Under 35 U.S.C. § 102(e)

The Examiner has rejected claims 145, 147, and 154 under 35 U.S.C. § 102(e), as allegedly being anticipated by Freeman *et al.* (U.S. Patent No. 6,605,279). Specifically, the Examiner alleges that "Freeman *et al.* teaches methods of downregulating or suppressing T cell mediated immune responses, including the use of B7-1-specific and B7-2-specific antibodies in conjunction with other immunomodulating reagents such as cyclosporine or FK506, including it *(sic)* usefulness in situations of tissue and organ transplantation as well as in GVHD (see entire document, particularly Other Therapeutic Reagents on columns 32-34)."

Applicants respectfully traverse the rejection. As the Examiner has admitted, "Freeman *et al.* differs from the claimed methods by not disclosing the well known use of immunosuppressives such as rapamycin and effective therapeutic antibody dosages in transplantation therapeutic regimens at the time the invention was made" (page 12, paragraph 10 of the Office Action). Therefore, Freeman *et al.* does not teach or suggest each and every element of the claimed invention. Applicants therefore respectfully request reconsideration and withdrawal of the rejection.

Rejection of Claims 145, 147, and 154 Under 35 U.S.C. § 103(a)

The Examiner has rejected claims 145, 147, and 154 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Freeman *et al.* (U.S. Patent No. 6,605,279) in view of de Boer *et al.* (U.S. Patent No. 5,747,034[2]). Specifically, the Examiner contends that the deficiencies noted above for Freeman *et al.* is remedied by de Boer *et al.*, which "teach[es] the use of B7-specific antibodies in combination with immunosuppressive agents such as cyclosporin, FK506 and rapamycin (e.g., see column 14, paragraphs 2-3) in therapeutic amounts and modes of administration encompassed by the claimed invention (e.g., see column 16, paragraph 5) (see entire document)."

[2] The Examiner has listed U.S. Patent No. 5,757,034 as the patent corresponding to de Boer *et al.* Based on the Information Disclosure Statement filed February 3, 2003, Applicants believe that the Examiner intended to refer to U.S. Patent No. 5,747,034.

Applicants respectfully traverse the rejection. As the Examiner is aware, "[i]t is improper to combine references where the references teach away from their combination. *In re Grasselli*, 713 F.2d 731, 743, 218 USPQ 769, 779 (Fed. Cir. 1983) (The claimed catalyst which contained both iron and an alkali metal was not suggested by the combination of a reference which taught the interchangeability of antimony and alkali metal with the same beneficial result, combined with a reference expressly excluding antimony from, and adding iron to, a catalyst)" MPEP 2145.

De Boer *et al.* teaches away from the combination of anti-B7-1 and anti-B7-2 antibodies disclosed in Freeman *et al.* In doing so, de Boer *et al.* discloses "co-administration of a molecule that specifically binds to the B7-1 molecule but not to B7-2 or B7-3 and an immunosuppressive agent" (column 6, lines 37-39; emphasis added). Moreover, Example 14 in de Boer *et al.* is substantially dedicated to demonstrating the advantages of blocking only B7-1 signaling, in contrast to the blockage of B7-1 and B7-2 signaling in the instant claims. Indeed, in discussing the advantages of the disclosed B7-24 monoclonal antibody, de Boer *et al.* states that "signaling by B7-2 interaction with T cells is needed for tolerance" and "[w]ith the B7-24 antibody, this is not a problem because…it does not block B7-2" (column 28, lines 11-15; emphasis added). Finally, de Boer *et al.* states that "blocking both B7-1 and B7-2 does not result in alloantigen specific tolerance" (column 32, lines 51-52). These disclosures not only teach away from the combination of anti-B7-1 and anti-B7-2 antibodies disclosed in Freeman *et al.*, but the latter statement is in direct contrast to the Applicants' results, showing that treatment with antibodies to B7-1 and B7-2 prolongs survival in comparison to treatment with either antibody alone (see Example 23, pages 104-108, and Figure 28 of the specification). Applicants therefore respectfully request reconsideration and withdrawal of the rejection.

CONCLUSION

Early and favorable reconsideration of the application is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned at (617) 832-1000. If any fees are due, the Commissioner is hereby authorized to credit any overpayment or charge any deficiencies to **Deposit Account No. 06-1448, WYS-004.01.**

Respectfully submitted,
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